REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the Claims

Claims 1 and 26 have been amended to clarify that all subsequent administrations of the first immunization occurs between two and six days after the first administration. Support for this amendment can be found, *inter alia*, in paragraph [0023] of the published application and in original claim 4. Claim 9 has been amended to correct a typographical error. The status identifiers of claims 15-17, 22-25 and 28 have also been updated, as requested by the Examiner.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-3, 5-14, 18-21, 26 and 27 a are now pending in this application, of which claims 15-17, 22-25 and 28 are withdrawn.

II. Objections to the Specification

The Examiner objected to the abstract for failing to be provided on a separate sheet. A replacement abstract is provided on a separate sheet herewith in compliance with M.P.E.P. § 608.01(b). Entry of this replacement abstract and withdrawal of the objection is respectfully requested.

III. Claim Objections

The Examiner has objected to claim 2 as being improperly dependent for allegedly failing to further limit the subject matter of a previous claim. Applicants respectfully traverse this objection.

The range specified in claim 2 refers to the days between administrations *within* each immunization, not between the first and second immunizations as apparently understood by the Examiner. The first immunization comprises at least two administrations, and all subsequent administrations must occur between 2-6 days after the first administration. Thus, all administrations of the first immunization occurs within 6 days of the first administration. Likewise, the second immunization may have more than one administration, and the subsequent administrations may occur between 2-6 days after the first administration of the second immunization. As recited in claim 1, the time between the first and second immunizations remains from 21-365 days. As discussed in the specification, the "clustering" of the administrations in these time frames provide for a surprising enhanced effect.

Because claim 2 further limits claim 1, it is in proper dependent format. Applicants respectfully request that that the objection be withdrawn.

IV. Claim Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-3, 5-14, 18-21, 26 and 27 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

A proper analysis of the enablement requirement of 35 U.S.C. § 112, first paragraph, begins with a determination of the subject matter encompassed by the claims. *See* MPEP § 2164.08 ("All questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims.") Applicants assert that the art provided by the Examiner as allegedly showing the unpredictability of the art does not apply to the present claims.

For example, on pages 5 and 8 of the Office Action, the Examiner discusses the Janeway reference, which describes antibody responses to antigens A and B. Applicants respectfully draw the Examiner's attention to the claims, which are drawn to a method for eliciting a T-cell response. Thus, the Examiner's analysis based on antibody responses is

inapplicable. As shown in Exhibit A, attached hereto, antibodies are produced by B cells, not T cells, and the activation pathway for the humoral (antibody) response is very different from that of the cellular (T cell) response. It is well known in the art that antigens are processed and presented differently for activation of the different types of responses, and different cytokines and helper cells are involved. Therefore, the discussion on page 8 of the Office Action regarding the lag phase of antibody responses cannot be applied to the present claims because it is discussing an entirely different mechanism.

Further, Applicants note that the claimed methods are for eliciting a T cell response against a T cell epitope, and it is this T cell epitope that is encoded by the administered NOI as well as provided in the protein-based second immunization. Therefore, once again, the Examiner's analysis based on administering different antigens, such as on page 8 of the Office Action, reciting antigens A and B, is not applicable to the present claims.

Likewise, on page 5 of the Office Action, the Examiner cites Rasmussen as evidence for showing the alleged unpredictability of the art because the authors found little CTL response in animal studies with their vaccination protocol. However, the study illustrated in Rasmussen is inapplicable, as the administered DNA does not correspond to the protein antigen boost, as required by the claims. As shown on page 41, beginning under the heading "Materials and Methods", Rasmussen administers five types of DNA encoding SIV gag/pol, SIV nef, HIV-HXB-2 particles, HXB-2 gp140, HXB-2 env and HXB-2 gp120. However, the protein boost administered 10 months later is HIV- IIIB gp160. None of the DNA administered is from the IIIB isolate of HIV, much less encodes the IIIB gp160. Not only is this protocol outside the scope of the present claims, one of skill in the art would not be surprised to find little or no cross-reactivity between the envelope proteins different HIV strains as well as between HIV and SIV, two different viruses altogether. Further, the protocol used by Rasmussen does not use the clustering administration technique as claimed, and the failure to detect CTL response merely supports Applicants' position that the clustering administration is a surprising improvement over the prior art techniques.

Furthermore, the Examiner's attempt to use Doria-Rose (discussed in more detail below) and U.S. Pat. No. 6,500,432 (Dalemans) is confusing. See page 5 of the Office

Action. It appears that she is stating that one of skill in the art would know that various optimization steps may be required for different antigens, as taught by Doria-Rose. Inasmuch that optimization is routine for one of skill in the art, Applicants agree; however, none of the cited art disclose the claimed features of the present invention, namely the clustering administration, nor the surprising T cell response. The Examiner questions why Applicants do not use the methods of Dalemans, and the answer is simply Applicants' methods are distinct from Dalemans. Applicants have found a surprising enhanced effect with the claimed clustering administration, while Dalemans does not use clustering and also provides a protein boost in a much shorter time frame than Applicants (1-10 days, as opposed 21-365 days as claimed).

Applicants remind the Examiner that it is not incumbent upon Applicants to explain why every possible method outside the scope of the claimed invention does not apply.

Regarding the lack of working examples provided in the present specification, Applicants note that such is not required to fulfill the requirements of 35 U.S.C. § 112, first paragraph, as discussed in M.P.E.P. § 2164.02. As discussed in detail in Applicants' Response filed November 21, 2008, Examples 3-5, 13 and 15 provide working examples for use of the clustering techniques, and the protein-based second immunization is disclosed, *inter alia*, in paragraphs [0110]-[0128] and [0135]-[0137]. While a working example showing the protein boost is not provided, one of skill in the art readily would have been able to provide the claimed second immunization using the information provided in the specification, and preliminary experiments provided in the examples indicated the claimed optimal time frame for the second immunization. Every element of the claims is well supported in the specification, both in the disclosure and in the Examples.

As one of skill in the art would be able to make and use the claimed invention, the specification enables the present claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

V. Claim Rejections Under 35 U.S.C. § 103

i. Billaut-Mulot in view of Janeway

Claims 1-3, 5, 8, 9, 11, 25, 18-20, 26, 27 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Billaut-Mulot (Vaccine 2001;19:95-102), in view of Janeway (Immunobiology 2001). Applicants respectfully traverse this rejection.

To establish a *prima facie* obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Applicants assert that this burden has not been met.

The claims require that the first immunization have at least two administrations, and that all subsequent administrations be given at least two and no more than six days apart. This interval is important to the surprising enhanced T cell response, such as demonstrated in Examples 13 and 15, which compare the clustered administrations using a four day interval or two day interval, respectively, versus the conventional administration methods.

Billaut-Mulot, as acknowledged by the Examiner on page 10 of the Office Action, does not teach immunizations with administrations between 2-6 days. The Examiner alleges that Billaut-Mulot "differs from instant claims in that the interval for administration of NOI was 7 days apart, not 6 days apart." Office Action, page 10. Applicants submit this is an incorrect reading of the reference. Instead, Billaut-Mulot teaches administrations of the plasmid over 21 days, by virtue of three weekly administrations, followed by a boost at 14 weeks. This reference in no way teaches that a T cell response can be primed by cluster administrations of the NOI within 2-6 days total.

Janeway also fails to teach this surprising aspect of the invention. The Examiner asserts that Janeway allegedly shows that it was well known that lymphocytes duplicate themselves rapidly for 3-5 days after activation. However, Janeway does not show that repeat administration of the NOI would increase that activation. Janeway teaches after a single antigen (not NOI, nor prime/boost) presentation, the lymphocyte divides rapidly to generate 1000 daughter cells within 3-5 days. See Janeway, § 1-12, third paragraph of the excerpt cited by the Examiner. There is no discussion of the effects of repeat administration for eliciting a T cell response during a 2-6 day time frame. One of skill in the art, after reading

Janeway, would have no reason to believe repeat administration during this initial expansion would increase the effectiveness of the immunization, or, in fact, be desirable at all.

Therefore, Janeway cannot be combined with Billaut-Mulot to teach a method for eliciting a T cell response against a T cell epitope comprising a first immunization comprising at least two administrations of a NOI administered between 2 and 6 days after the first administration, followed by a second immunization of the epitope 21 to 365 days after the first administration of the first immunization. Neither reference, either alone or in combination, provide these teachings. Accordingly, Applicants respectfully request that the rejection be withdrawn.

ii. Billaut-Mulot in view of Janeway in further view of Doria-Rose

Further, claims 6, 7, 10, 12 and 13 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Billaut-Mulot in view of Janeway as applied to claims 1-3, 5, 8, 9, 11, 14, 18-20, 26 and 27, further in view of Doria-Rose (Methods 2003;31:207-16). Applicants respectfully traverse this rejection.

The Examiner applies Billaut-Mulot in view of Janeway as discussed above and adds Doria-Rose as allegedly establishing the general state of the art of combined DNA and protein vaccinations. The Examiner points to Table 1 of Doria-Rose as providing examples of successful DNA-protein vaccinations, but Applicants note that no where does this reference disclose a method using clustered administrations as presently claimed. Indeed, as noted in Applicants' Reply filed November 21, 2008, the only examples of specific dosing regimens provided in Doria-Rose, Table 2 and Figure 1, show administrations that occur over multiple weeks, not 2-6 days as claimed. Thus, Doria-Rose teaches away from using clustered administrations (i.e., multiple administrations within 2-6 days as claimed) by motivating one to use an interval of DNA administration greater than even that disclosed in Billaut-Mulot. Furthermore, in both examples of Doria-Rose, the antibody titers were measured to gauge antibody response, not the T cell response as recited in the present claims. See Doria-Rose, page 213, left column, first partial paragraph.

The Examiner alleges that the 2-6 day limitation is within the bounds of optimization because the specification allegedly fails to compare this limitation to a 7-14 day time frame. Office Action, page 14. However, Applicants vigorously disagree. First, as stated before, it is the Examiner's burden to present a prima facie case of obviousness by showing all the claim limitations are taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Therefore, it is the Examiner's burden to show the art teaches or suggests the 2-6 day time frame, which Applicants assert she has failed to do. As recited in the claims, the second and subsequent administrations occur 2-6 days after the first administration, not in 2-6 intervals from each other. None of the art cited by the Examiner teaches or suggests administration of the NOI in less than 21 days, which is more than three times longer than the claimed time frame. This difference is not trivial, and Applicants' methods lead to the enhanced immune response discussed throughout the specification, as noted previously. As the Examiner not cited art that teaches or suggests this much shorter time frame, much less in conjunction with the other elements of the claims, she has failed to meet her burden for establishing a prima facie case for obviousness.

Therefore, because the cited art does not teach all the limitations of the claims, either alone or in combination, it cannot render the present claims obvious. Accordingly, Applicants respectfully request that the rejection be withdrawn.

iii. Billaut-Mulot in view of Janeway in further view of Berglund and Horvath

The Examiner also rejects claim 21 under 35 U.S.C. § 103(a) as allegedly obvious over Billaut-Mulot in view of Janeway as applied 1-3, 5, 8, 9, 11, 14, 18-20, 26, 27 above, further in view of Berglund et al (Vaccine 1999; 17:497-507), and Horvath (Immunol Lett 1998; 60:127-36). Applicants respectfully traverse this rejection.

The Examiner applies Billaut-Mulot in view of Janeway as discussed above and adds Berglund and Horvath as allegedly teaching using DNA prime and protein boost for influenza vaccination or multiple influenza antigens. The deficiencies of the primary references are discussed in detail above, and the secondary references do not overcome these deficiencies. Neither reference teaches the cluster administration of the NOI as recited in the claims, nor is

the recited timing within the bounds of optimization as asserted by the Examiner. Berglund teaches immunizing mice with Semliki Forest Virus encoding LacZ or NP, followed by a second immunization with the same virus two weeks later. *See* Results, section 3.1 beginning on page 499 and section 3.3 beginning on page 501. Thus, neither immunization with NOI followed by a protein, nor the claimed time frames for administration is taught or suggested by Berglund.

Likewise, Horvath merely discloses administration of the HA peptide in a single dose. Neither Doria-Rose, Berglund nor Horvath teach or suggest first immunization with a NOI comprises at least two administrations of a NOI encoding the T cell epitope over 2-6 days, followed by a second immunization with a protein comprising the T cell epitope. To the extent that any reference may teach the administration of nucleotide followed by a protein, they teach that the nucleotide should be administered at intervals much longer than those presently claimed. Because none of the references, alone or in combination, teach or suggest the present invention, they cannot render the present invention obvious. Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the

Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Aug 3, 2009

By

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4792
Facsimile: (202) 672-5399

Jacqueline D. Wright Bonilla
Attorney for Applicants
Registration No. 45,239

EXHIBIT A

Senior editor:	Deborah Allen
Development editors:	Michelle Russel Julet and Diane Cimino Maass
Project editor:	Diane Cimino Maass
Line editor:	Ruth Steyn
Cover and text designer:	Marsha Cohen/ Parallelogram Graphics
Illustration coordinator:	Susan Wein
Illustration:	Network Graphics
Production coordinator:	Sheila E. Anderson
Composition:	Sheridan Sellers/W. H. Freeman Electronic Publishing Center
Manufacturing:	Von Hoffman Press, Inc.

ABOUT THE COVER AND FRONTISPIECE

Interactions of cell adhesion molecules, with different ones involved at different times, are responsible for recruiting leukocytes to inflammatory sites and for their migration through the vascular endothelium. Slowed by vasodilation, leukocytes drift against vessel walls, where selectins are responsible for a loose adherence known as "rolling." This initial step in leukocyte migration is shown in a false-color scanning electron micrograph. (See Chapter 15 for more information.)

Library of Congress Cataloging-in-Publication Data

Kuby, Janis.
Immunology / Janis Kuby. — 3rd ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-7167-2868-0
1. Immunology. I. Title.
[DNLM: 1. Immune System. 2. Immunity. QW 504 K95i 1997]
QR181.K83 1997
616.07'9 — dc21
DNLM/DLC
for Library of Congress 96-52442
CIP

Printed in the United States of America

First Printing, 1997

Visualizing Concepts